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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,181	09/24/2003	Caroline Osterhoff	35-268	5220

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EXAMINER	
ULM, JOHN D	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,181	OSTERHOFF ET AL.	
	Examiner	Art Unit	
	John D. Ulm	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17,19-30 and 33* is/are pending in the application.

4a) Of the above claim(s) *6-14 19 20 22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,17,21 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1) Claims 1 to 14, 17, 19 to 30 and 33 are pending in the instant application. Claims 1 to 9, 17, 21 to 23, 26, 27, 30 and 33 have been amended and claims 31 and 32 have been canceled as requested by Applicant in the correspondence filed 15 February of 2007.

2) Any objection or rejection of record that is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

4) A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 February of 2007 has been entered.

Election/Restrictions

5) Claims 6 to 14, 19, 20 and 22 to 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the correspondence filed 05 October of 2005. Claim

22 has been withdrawn because it has been amended to recite a method treatment whereas the elected invention is an isolated polypeptide.

Claim Rejections - 35 USC § 101

6) Claims 1 to 5, 17, 21 and 33 are rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed specific and substantial credible utility for those reasons of record as applied to claims 1 to 5, 17, 21 and 22 in section 3 of the office action mailed 29 November of 2005. As stated therein, the instant claims are drawn to an isolated mammalian epididymis-specific receptor polypeptide that lacks a specific and substantial utility in currently available form because the instant application does not disclose an established specific biological role for the claimed polypeptide or its significance to a particular disease, disorder of physiological process which one would wish to manipulate for a desired clinical effect.

Applicant has traversed this rejection on the premise that it conflicts with Example 6 of the Synopsis of Application of Written Description Guidelines. Applicant is advised that Example 6 of the Synopsis of Application of Written Description Guidelines is completely silent on issues involving utility.

Applicant has again traversed the instant rejection on the basis that the claimed polypeptide has utility as an epididymis-specific tissue marker and that the employment that polypeptide as an epididymis tissue marker is a specific and substantial utility. The production of subtractive libraries to isolate cDNAs encoding proteins which are expressed in a tissue-specific or developmentally-specific manner was a practice that was old to the art of molecular biology by the time that the instant invention was made.

It is now believed in the art that the human genome encodes approximately 30,000 protein, of which only about 5,000 are "housekeeping" proteins which are not expressed in a tissue-specific or developmentally-specific manner. This means that five out of six proteins in the human body are expressed in a tissue-specific or developmentally-specific manner and the isolation of a cDNA encoding a protein having a desired tissue expression pattern requires nothing more than the routine practice of the art. Therefore, the employment of a particular protein simply as a marker for the tissue in which it is expressed is no more of a specific and substantial utility than the employment of that protein as a molecular weight marker in an analytical process simply because it has a molecular weight which is different from the molecular weights of most other proteins.

The declaration by Ulrich Gotwald under 37 CFR 1.132 which was filed 24 September of 2003 is insufficient to overcome the rejection of claims 1 to 5, 17, 21 and 31 to 33 based upon a lack of specific and substantial utility as set forth in the last Office action because it fails to establish a specific and substantial utility for the claimed protein in currently available form. This declaration described the production of transgenic mice in which the murine ortholog of the claimed protein has been eliminated. This declaration shows that the complete abolition of a protein of the instant invention from a male mammal results in a reduction in the fertility of that mammal. This evidence does not appear to support a conclusion that the administration of a protein of the instant invention, or antibodies thereto, to a mammal will effect the fertility of that mammal.

The protein of the instant invention is a member of the G protein-coupled receptor family. There is not a single reference of record describing the administration of a G protein-coupled receptor or antibodies to a G protein-coupled receptor to an organism to achieve a clinical effect. At best, one of ordinary skill in the art would conclude from the Gotwald declaration that a protein of the instant invention may serve as a target for antagonists thereto, which might be expected to reduce the fertility of a male mammal to which they were administered. However, before one can identify an antagonist to the claimed protein one must know the identity of at least one agonist to that receptor protein and at least one measurable physiological parameter which is influenced by the binding of that agonist to the receptor. Unless one can measure the activity of the claimed protein one can not identify compounds which inhibit that activity (antagonists). Therefore, one would conclude that a protein of the instant invention will ultimately have the practical utility of being employed to identify compounds which reduce male fertility. However, a claimed invention must have a practical utility in currently available form and a protein of the instant invention can not be employed to identify antagonists thereto until one has made the substantial inventive contribution of discovering the identity of at least one agonist to that receptor protein and at least one measurable physiological parameter which is influenced by the binding of that agonist to the receptor.

Further, one would not reasonably expect that the administration of an antibody to a protein of the instant invention to an individual would result in a reduction of that individual's fertility. The Chuntharapai et al. publication (Methods in Enzymology

288:15-27, 1997, cited by Applicant) describes the production of antibodies to that class of G protein-coupled receptors known as the chemokine receptors. This reference discloses that the production of "blocking" antibodies, which prevent the activation of a selected receptor by its respective ligand, was only accomplished by immunizing a mouse with a cell expressing the selected receptor and then screening the subsequently produced monoclonal antibodies for those which could actually antagonize that receptor. This reference shows that most of the antibodies produced against a particular G protein-coupled receptor will not antagonize that receptor. It supports the conclusion that an artisan must know the identity of at least one agonist to a receptor protein and at least one measurable physiological parameter which is influenced by the binding of that agonist to the receptor before that artisan can identify those antibodies in a hybridoma library which are antagonistic for a given receptor.

Any assertion that the knock-out mice described in the Gotwald declaration are representative of a naturally occurring disease or disorder would not be supported by the evidence of record. The fact that one can create a tissue-specific disorder by eliminating a tissue-specific gene product does not support a conclusion that a naturally occurring disorder reflecting a similar disfunction is the consequence of a similar genetic defect. It is well known in the art that different forms of diseases such as hepatitis and meningitis have common symptoms resulting from diverse causes. There is no evidence currently of record that a reduced fertility in certain human males results from an altered structure or pattern of expression of a protein of the instant invention. Further, Applicant's argument that the detection of a protein of the instant invention in a

sample can be employed to quantitate e epididymis and, consequentially, diagnose infertility is not supported by the instant specification or the art of record. Nowhere in the instant disclosure can one find a credible assertion that infertility of any kind is associated with a reduction in the volume or mass of epididymis in humans. Therefore, one would not conclude that the quantitation of epididymis is useful in the diagnosis of infertility.

Applicant urges that there is an abundance of scientific literature outlining a role of human epididymis specific protein (ESRP) of the instant invention in spermatogenesis. The claimed polypeptide lacked specific and substantial utility at the time that the instant application was filed because neither the prior art of record nor the instant specification had identified a specific and substantial established utility for that protein or identified its specific role in spermatogenesis. Applicant can not rely upon those discoveries made by themselves or others subsequent to the filing of the instant application to establish or reasonably confirm a practical utility for the claimed invention. It is a matter of law that an invention must have a specific and substantial utility "in currently available form", which precludes the need for further research, if that research is needed to establish a utility for the claimed invention (*Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966)).

Claim Rejections - 35 USC § 112

7) Claims 1 to 5, 17, 21 and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the instant invention for those reasons given above with regard to the rejection of these claims under 35 U.S.C. § 101.

8) Claims 1 to 3, 5, 17 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of a protein comprising the amino acid sequence presented in SEQ ID NO:2 of the instant specification wherein that protein "is intracellularly coupled to a G protein and has G-protein signal transduction activity", it does not reasonably provide an adequate written description of any other polypeptide which meets both the structural and functional recited in these claims, or the guidance needed to make it. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 1, for example, encompasses an isolated polypeptide comprising as few as ten amino acids from SEQ ID NO:2, wherein that polypeptide protein "is intracellularly coupled to a G protein and has G-protein signal transduction activity". The instant specification, however, fails to disclose a ligand for a polypeptide comprising the entire amino acid sequence of SEQ ID NO:2 and fails to demonstrate any measurable biological activity for that protein. It is only **assumed** to have activity because it appears to be a naturally occurring member of the G protein-coupled receptor family. The amino acid sequence presented in SEQ ID NO:2 of the instant application is 1038 amino acids in length. Claim 1 only requires one to retain ten contiguous amino acids from that sequence. The claims are not enabled because an artisan does not have a reasonable expectation that a protein whose amino acid sequence has been altered or deleted by up to 90% is going to retain functionality or structural integrity.

Whereas the instant claims potentially encompass tens of thousands, if not millions, of naturally and non-naturally occurring structural embodiments, the instant specification only describes one working example of an isolated naturally occurring protein, and the functionality of that protein is unproven. The instant specification does not provide even one working example of a functional receptor protein of the instant invention whose amino acid sequence deviates from nature by as little as a single amino acid sequence, much less the 938 residues permitted by claim 1. Further, the instant specification does not identify those amino acid residues in the amino acid sequence of SEQ ID NO:2 which are essential for the biological activity and structural integrity of a receptor comprising that sequence and those residues which are either expendable or substitutable, nor does it identify a structurally related protein in the prior art for which this information is known and could be applied to the claimed protein by analogy. In the absence of such structure-function information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of over 1000 amino acid residues before they could even begin to rationally design a functional receptor polypeptide having other than that single natural amino acid sequences presented in the specification. And this structure/function analysis could only begin after that practitioner has made the substantial inventive contribution of discovering the identity of a compound that activates that single, naturally occurring protein and discovering the identity of a signal transduction activity mediated thereby.

As disclosed in the instant specification, a protein of the instant invention is presumed to be a member of the G protein-coupled receptor family because the amino qacid sequence of SEQ ID NO:2 appears to have certain structural features that are characteristic of this protein family. By definition, all of the proteins belonging to this family share a complex serpentine structure comprising four extracellular domains, seven transmembrane domains and four cytoplasmic domains. The ligand binding activity of the subfamily of receptors to which the instant invention belongs, which includes adrenergic and dopamine receptors, is generally attributed to interactions between a ligand, various amino acid side chains extending from several different extracellular and transmembrane domains and the hydrophobic pocket formed by those transmembrane domains. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Given the complex structure of a protein of the instant invention, and the lack of working examples and guidance in the predictable alteration of such proteins, and artisan could not reasonably produce an isolated polypeptide of the instant invention whose amino acid sequence deviates from that single sequence recited in the claims by even a single amino acid residue and reasonably "predict by resort to known scientific law" whether that protein will function retain signal transduction activity as required by the instant claims.

Further, these claims encompass subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims encompass, for example, an "isolated" "polypeptide having at least 90% sequence similarity to the amino acid sequence set forth in SEQ ID NO:2" wherein that polypeptide "is intracellularly coupled to a G protein and has G-protein signal transduction activity". It is a routine matter for an artisan to identify those members of the genus of nucleic acids which meet the material limitations of being an "isolated polypeptide" and "polypeptide having at least 90% sequence similarity to the amino acid sequence set forth in SEQ ID NO:2"". However, one of ordinary skill would not reasonably expect that the majority of polypeptides belonging to that genus to also meet the limitation ""is intracellularly coupled to a G protein and has G-protein signal transduction activity". One would not reasonably expect the functional limitation of the instant claims to inherently flow from the structural limitations recited therein. Further, the instant specification does not identify that physical or structural property of

combination of physical or structural properties that can be used to distinguish those polypeptides which meet the functional limitation of the claims from those that don't. The inclusion of a functional limitation in the claims in the absence of a recitation of those material features which provide that function constitutes nothing more than a wish to know the identity of any nucleic acid which meets all of the limitations of the claims. In the decision *The Regents of the University of California v. Eli Lilly and Company,* 43 USPQ2d 1398 (CAFC 1997), the court held that:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

Whereas the instant specification provides a detailed description of a single naturally occurring protein that is presumed to meet all of the limitations of the claims, the instant specification does not provide a written description of the genus of polypeptides encompassed thereby or even a representative number of the potentially tens of thousands, or millions, of non-naturally occurring embodiments currently claimed.

9) Claims 1 to 3, 5, 17 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9.1) Claim 1 is vague and indefinite because the metes and bounds of the limitation "6S°C" are uninterpretable. This limitation is not described in the specification nor is it an art recognized term. Claims 2, 3, 5, 17 and 33 are vague and indefinite in so far as they depend from claim 1 for this element.

9.2) Claim 2 is vague and indefinite because there is no antecedent basis for "the hydrophilic region of said receptor". As demonstrated by Figure 8 of the instant application, the amino acid sequence of SEQ ID NO:2 contains a plurality of hydrophilic and hydrophobic regions. Claim 3 is vague and indefinite in so far as it depends from claim 2 for this element.

Claim Rejections - 35 USC § 102

10) Claims 1 to 5, 17, 21 and 31 to 33 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by the Osterhoff et al. publication (DNA and Cell Biol. 16(4):379-389, Apr. 1997). Applicant is advised that, because the previous application did not meet the "how to use" requirement of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention, it is unavailable to the instant application under 35 U.S.C. § 120.

Response to Arguments

11) Applicant's arguments filed 15 February of 2007 have been fully considered but they are not persuasive for those reasons given above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (571) 272-0880. The examiner can normally be reached on 9:00AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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